Test Data Protection: WHO perspective

Symposium On The Evolution Of The Regulatory Framework Of Test Data – From The Property Of The Intellect To The Intellect Of Property
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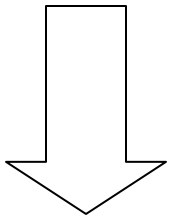
World Health Organization

Summary of the presentation

- Background
- Requirements for registration/marketing authorisation
- Test data and the TRIPS Agreement
- Test data from a regulatory perspective and public heath challenges
- Global Strategy and Plan of Action

Background: Medicines are subject to two sets of rules

Intellectual property rights



The right to exclude
but not to market or use

Background: Medicines are subject to two sets of rules

Intellectual property rights

The right to exclude

But not the right to market or to use

Registration requirements

Authorization for marketing approval based on set criteria

Marketing approval may be denied

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Background: Conditions of registration or marketing authorisation

- Submission of data based on quality, efficacy and safety
- Countries may rely on decisions of other well established regulatory authorities
- Basis of registration may include consideration of data that is in the public domain (this may be interpreted restrictively –Dodds-Smith, 2000)
- Publicly available reports
  - Summary Basis for Decision (Health Canada)
  - European Public Assessment Report (EMEA and EC Members)
  - Approval History and Related Documents (DRUG@FDA)
  - WHO Public Assessment Report (WHOPAR) and Public Inspection Report (WHOPIR)
- WHO designing a registration package to facilitate approval and also make information to be in a standardised and usable form

Background: Regulation of medical products

Medicines are among the most regulated products on the market

The aim is mainly to protect the public from harm and promote public health.

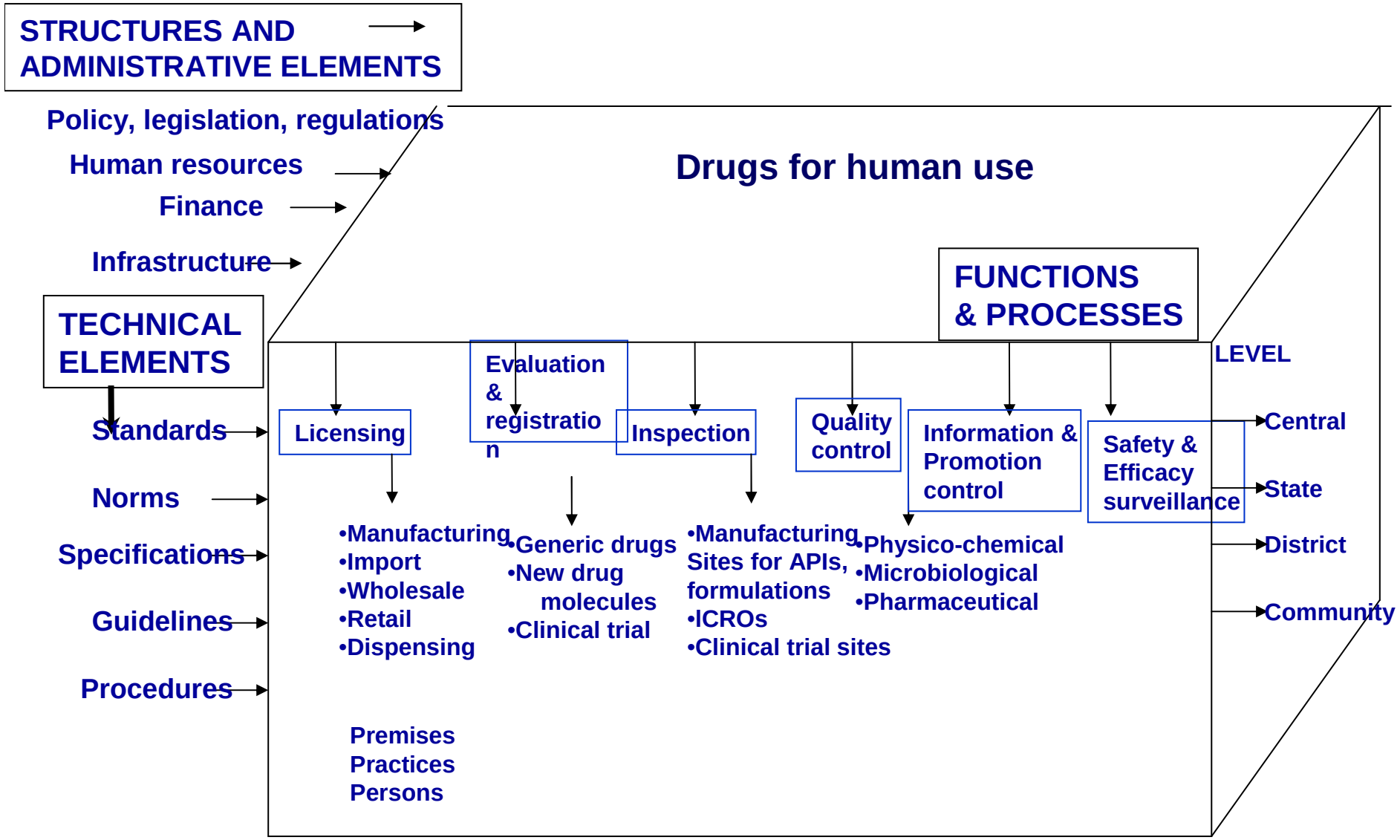
Medicines must meet standards of quality, safety and efficacy

Countries may decide which information accompanying an application for regulatory approval is confidential and which is not

Considerable effort is not one of the criteria considered for regulatory approval, only quality, efficacy and safety

Different set of regulation from patent laws

Dimensions of Drug Regulation



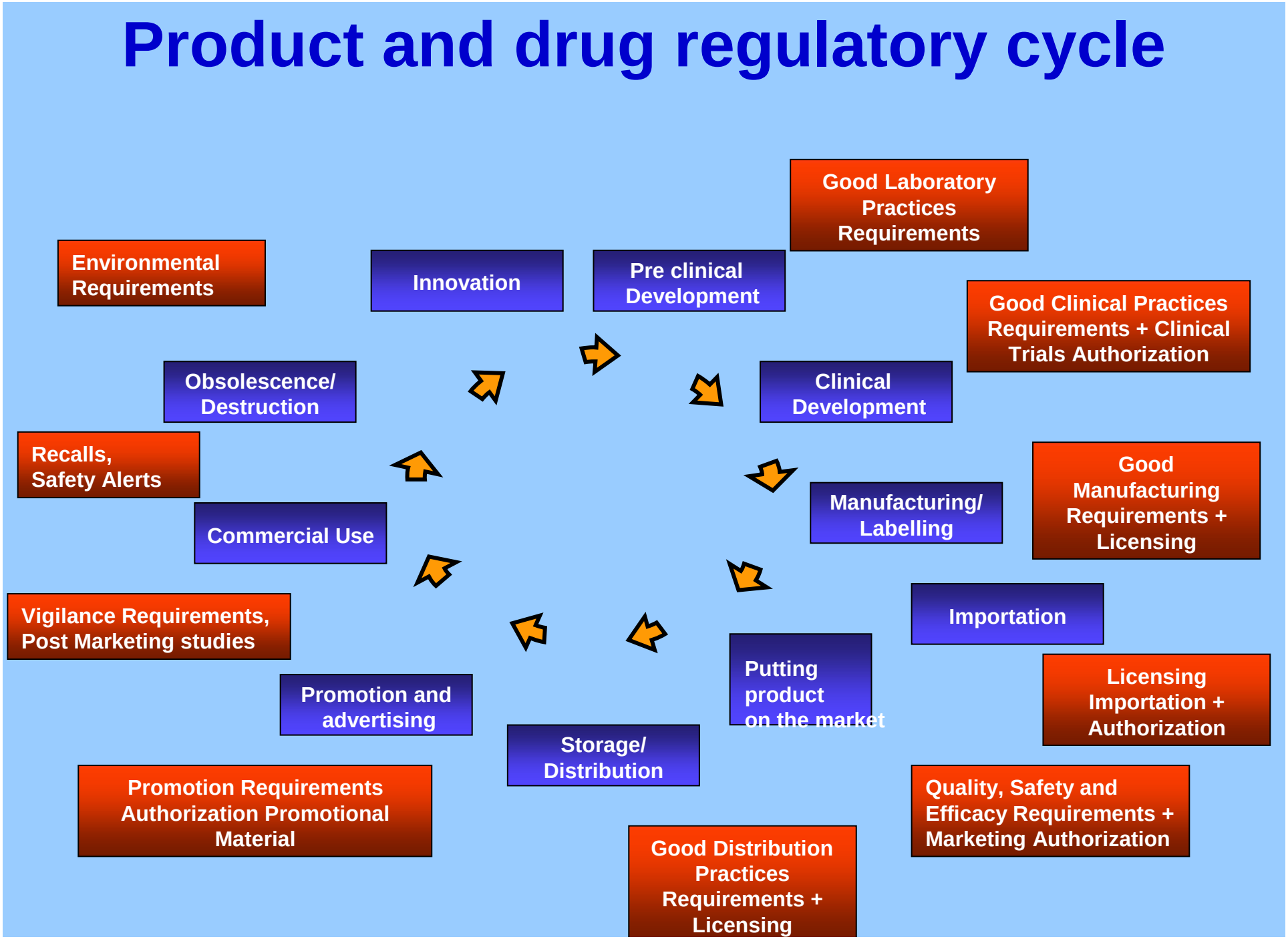
Survey in Sub-Saharan Africa

- The questionnaires developed were targeted at manufacturers of (12) generic medicines, (16) innovator products, (11) regulatory authorities, there were also interviews with individuals with extensive regulatory experiences from both a developed and developing country context, some of the issues raised:
  - No specific requirements for FDC's, vaccines, new dosage forms
  - Some require certain regulatory data others do not
  - Limited capacity has resulted in some requirements not implemented
  - Most rely on WHO prequalification for both drugs and vaccines
  - Poor responses to enquiries or requests for information
  - Poor quality of submissions
  - Insufficient data
  - Unsubstantiated claims

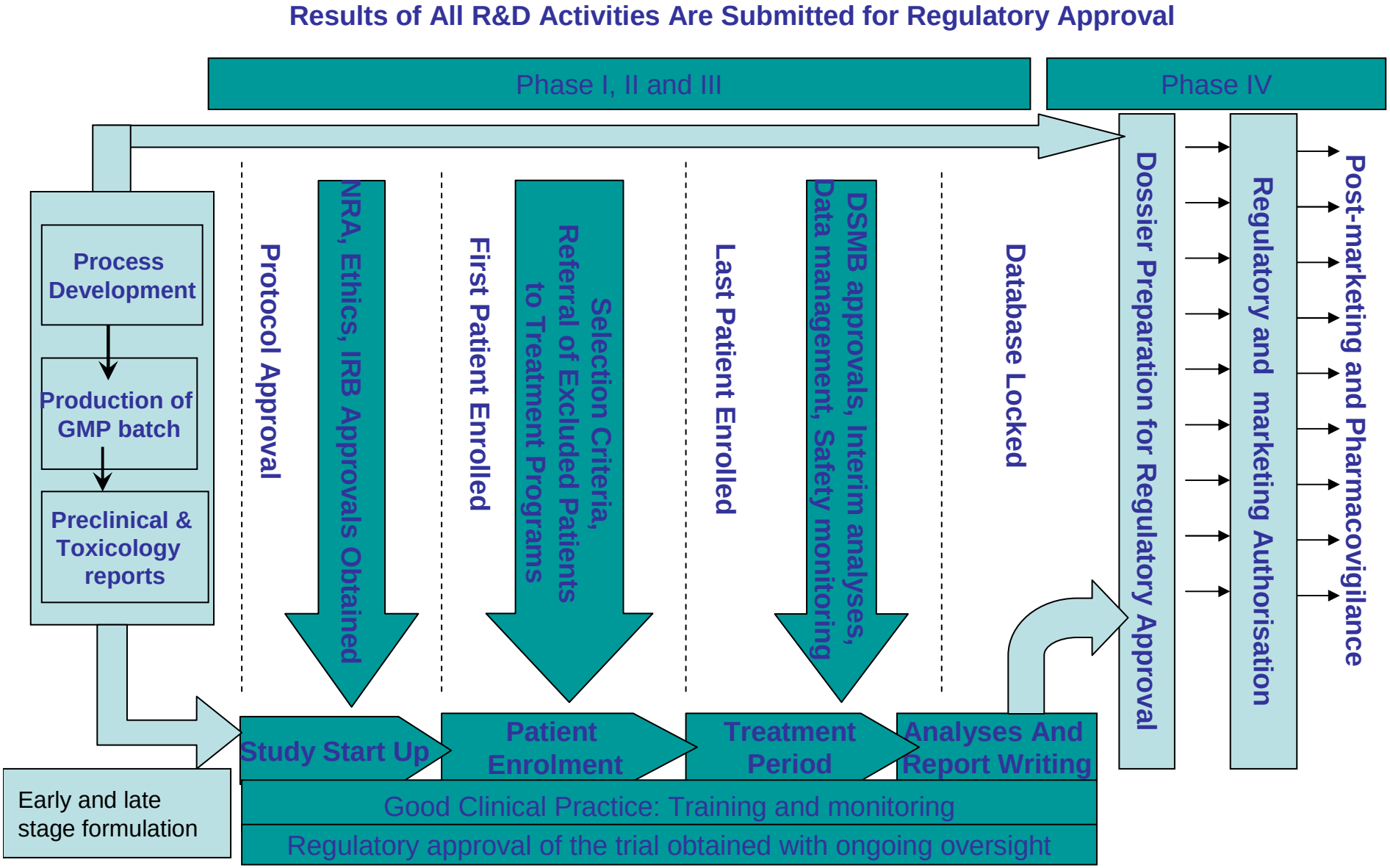
Article 39.3

- "Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use. In addition, Members shall protect such data against disclosure, except where necessary to protect the public, or unless steps are taken to ensure that the data are protected against unfair commercial use."

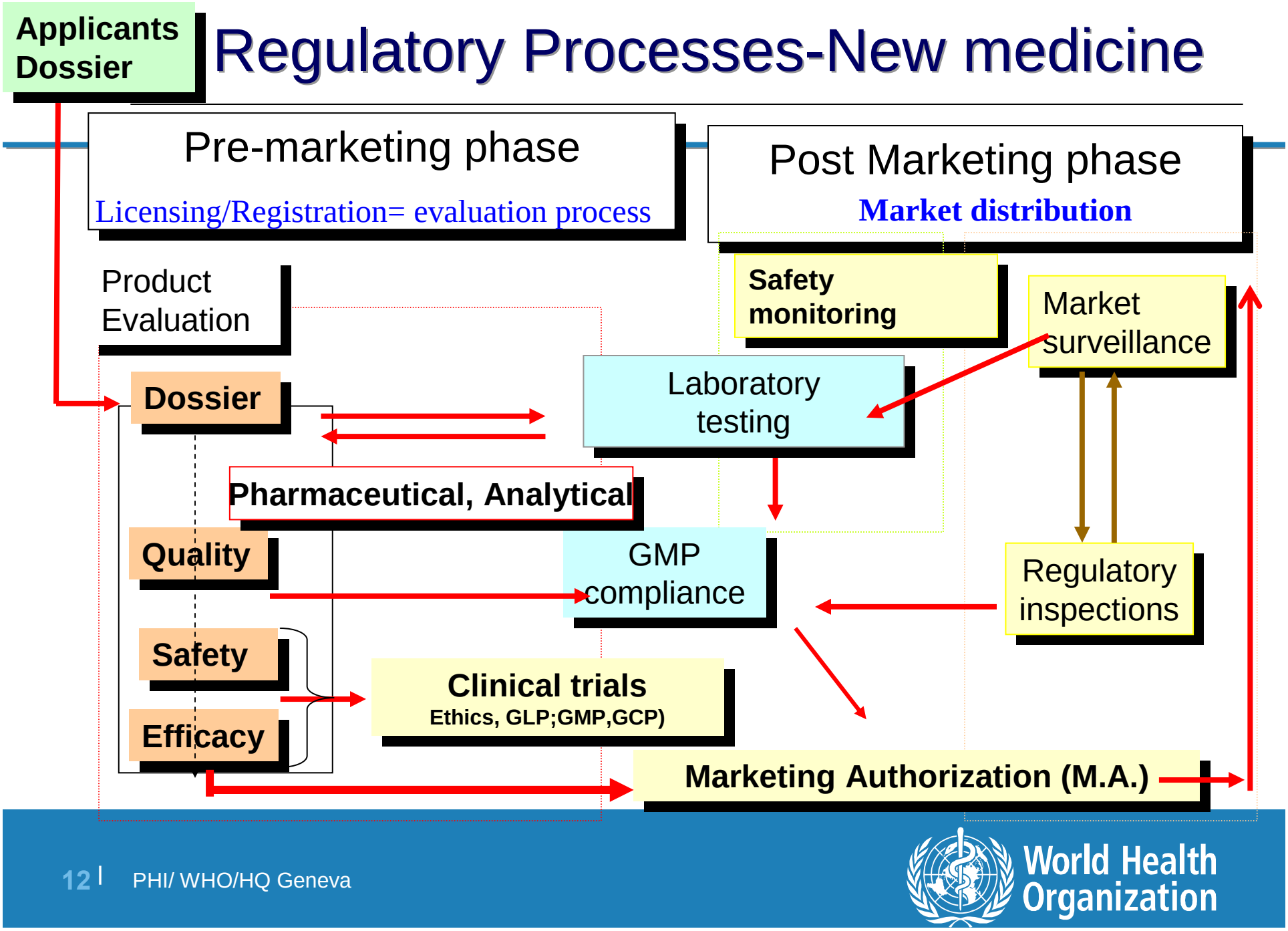
Product and drug regulatory cycle



The Pre-marketing activities and dossier submission



Regulatory Processes-New medicine



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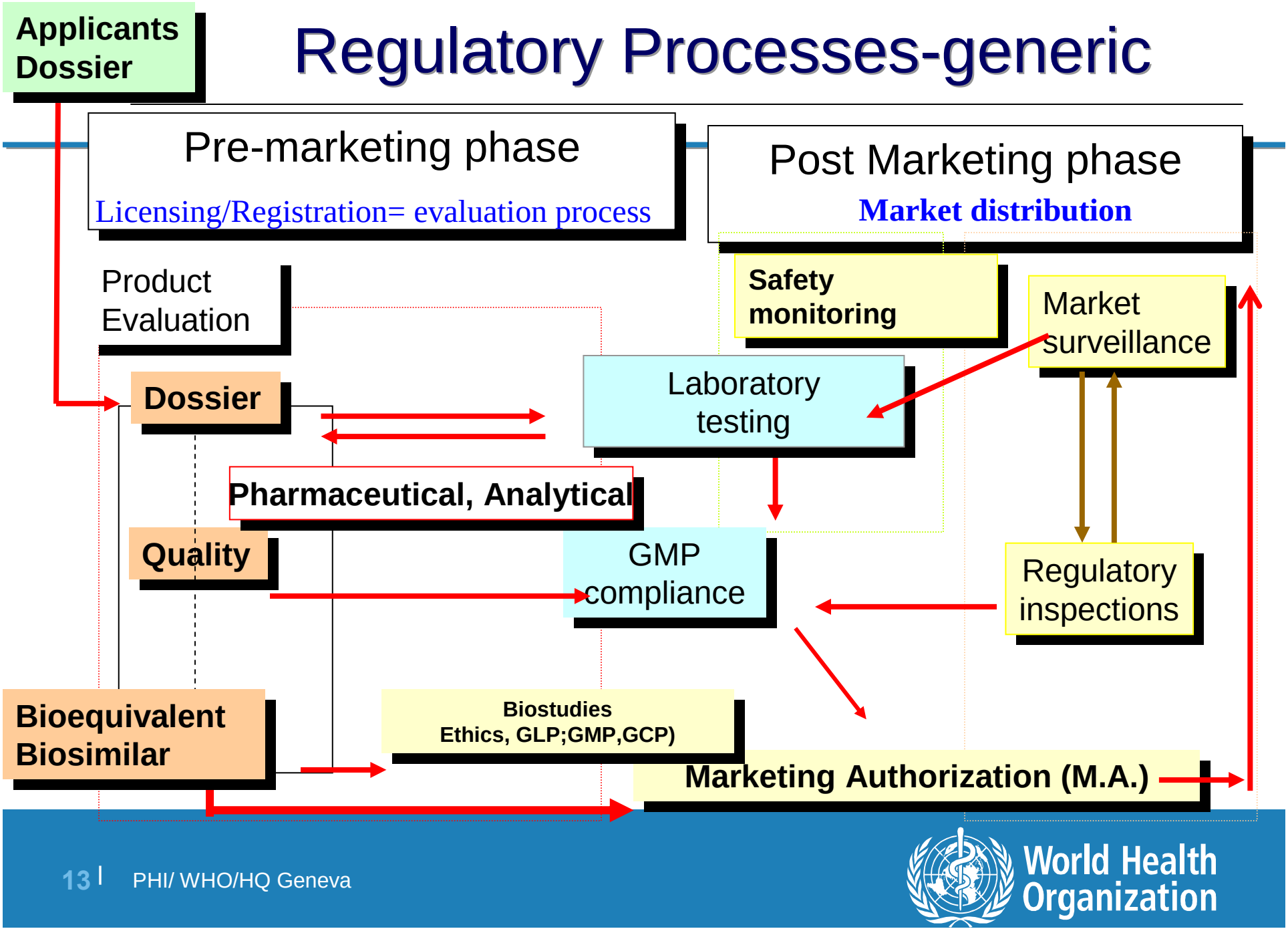
Regulatory Processes-generic



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Registration/Marketing authorisation

- **PRE-REGISTRATION ACTIVITIES**

- **PRELIMINARY EVALUATIONS**
  - Physical appearances
  - Labeling issues

- **CLINICAL TRIALS*****
  - Phase I
  - Phase II
  - Phase III

- **LABORATORY ANALYSIS**
  - Microbiological analysis
  - All physicochemical analysis and assays
  - Biological assays and tests

- **MARKETING AUTHORIZATION STEPS**

- **Dossier Evaluation**
  - Safety and Efficacy data
  - Pharmaceutical and Analytical data
  - Bioequivalence/ Comparative dissolution (Generics)
  - Accuracy of documentation
  - Approval of package insert which accompanies a product

- **Inspections**
  - GCP inspections
  - GMP compliance
    - Manufacturing Premises

Post registration activities

- **POST MARKET SURVEILLANCE**
  - Sampling and testing of marketed medicines
  - Investigations & Monitoring
  - Recalls
  - post marketing quality surveillance activities

VARIATIONS/CHANGES

Minor-changes,
Manufacturing changes
Major- formulation changes
New safety information
New indications, Site changes

PHARMACOVIGILANCE

- Adverse drug events
- Warning
- Quality Defects

- **CONSUMER EDUCATION/COMPLAINTS**
  - Promotion and advertising
  - Posters & brochures
  - Patient information leaflets
  - Channels of complaints
- **ENFORCEMENT & SANCTIONS**
  - Cautions
  - Bringing into compliance
  - Fines/Penalties
  - Prosecution

Clinical trials: Phases

- Phase I : Studies involving a new active ingredient or new formulation in healthy human volunteers
- Phase II: Studies performed in a limited number of subjects to show efficacy and assess short-term safety in patients suffering from a disease.
- Phase III: studies involving larger patient populations, to determine short-term to long-term safety/efficacy and overall and relative therapeutic value.
- Phase IV : studies performed post-marketing which may be designed to explore new indications, new methods of administration and new combinations. Sometimes purely for marketing purposes.

Test data and TRIPS Agreement: Article 39.3

- Prior to the TRIPS Agreement coming into force, countries relied on originator test data to approve generic products.
- Once test data was submitted by the originator, the regulatory authorities could rely on the data to approve subsequent applications on similar products, or to rely on proof of prior approval of a similar product in another country.
- Generic manufacturers need only to prove that their product is pharmaceutically identical to the original product or if it is bioequivalent.
- The active substance's efficacy and safety profile have been established for the innovator medicine,

Test data and TRIPS Agreement: Article 39.3

- It is generally not required to provide results of preclinical tests in animals and of clinical trials with a generic application.
- Approval of generic medicines may not be considered unfair commercial use from a public health perspective,
- WHO has promoted the concept of essential medicines based on generics for more than 30 years,
- The majority of products on the essential medicines list are generics

Test data and TRIPS Agreement: Article 39.3

- Article 39.3 TRIPS does not define the terms "unfair commercial use" and "new chemical entities" and does not prescribe how to protect the data against unfair commercial use and disclosure.
- Disclosure from a public health perspective may be crucial, particularly with respect to safety and for indications that are of major public health importance
- Countries may consider defining what can and cannot be disclosed, from a public health perspective this is important

Test data from a regulatory perspective and public health considerations

- Non-disclosure and confidentiality
- Prevention of misappropriation
- Confidentiality may pose public health challenges:
  - Concealment of safety data
  - Conduct of unnecessary trials for data that already exists
  - Public health priorities

Test data from a regulatory perspective and public health considerations

- Safety information should be shared and disclosed
  - regulatory measures have been introduced, where harm was caused
  - withdrawals of medical products from the market

    [From 1960-1999 there were 121 safety related drug withdrawals world-wide due to serious safety problems. 50% of these withdrawals were mainly in Europe, North America, Asia Pacific and the other from a market of multiple continents (Fung M et al,2000)]
  - amendments to package inserts and labelling in a form of warnings and precautions

    [Kesselheim and Avorn have also shown that information in the package insert or labelling information, can vary in its completeness and balance, there may be concealment, or adverse events may be understated or even excluded]

Test data from a regulatory perspective and public health considerations

- New indications that are important for public health purposes may be a consideration:
  - HIV /AIDS Experience- initially mono-therapy approach followed in treatment, subsequently combination therapy recommended
  - Prevention of mother to child transmission, an indication introduced subsequent to clinical trial data was made available
- WHO provides guidelines and essential drugs list which should be adapted for local use, particularly for public sector use and procurement, may not be affected by regulatory conditions of test data

Conclusion

Element 5 of the Global Strategy and Plan of Action: Application and management of intellectual property

5.1 (a) encourage and support the application and management of intellectual property in a manner that ***maximizes health-related innovation and promotes access to health products*** and that is consistent with the provisions in the TRIPS agreement and other WTO instruments related to that agreement and meets the specific R&D needs of developing countries

Conclusion

5.2 (b) take into account, where appropriate, the impact on public health when considering adopting or implementing ***more extensive intellectual property protection than is required*** by the Agreement on Trade-Related Aspects of Intellectual Property Rights, without prejudice to the sovereign rights of Member States

Countries can decide based on their needs, circumstances and the context with respect to what is ***necessary to protect public health***